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(54) Enteric microcapsules and process for the preparation thereof.

(57) Novel enteric microcapsules containing an active compound as a core material, the coating walls of which consist essentially of ethylcellulose and an enteric polymer material, and optionally a water-swellable polymer material being incorporated into the core material, and a process for the preparation thereof. The microcapsules can easily release the active compound in intestinal tract while protecting the core material sufficiently in stomach.

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ENTERIC MICROCAPSULES AND PROCESS FOR  
THE PREPARATION THEREOF

The present invention relates to novel enteric microcapsules and a process for the preparation thereof, more particularly, to enteric microcapsules containing an active compound as a core material, the coating walls of which consist essentially of ethylcellulose and an enteric polymer material, and a process for the preparation thereof.

It is known to control the release of a core material in microcapsules by thickening the coating walls of microcapsules or by forming compact coating walls and thereby decreasing the permeability thereof (cf. Tamotsu Kondo and Masumi Koishi; "Microcapsules, Process for the Preparation thereof, Their Properties and Applications", issued by Sankyo Shuppan, 1977). According to these known methods, however, while the release of core material is well controlled, the release of core material is also inhibited even when the core material should be released and hence the desired activities of the main active compounds are occasionally not obtained. Particularly, in case of pharmaceutical compounds, they are usually microencapsulated with ethylcellulose in order to mask unpleasant odor or taste thereof, but in most cases, such microcapsules show

retarded release of the active ingredient in intestinal tract.

From this viewpoint, the present inventors have extensively studied on improvement of microcapsules, and as a result, it has been found that the desired enteric microcapsules having excellent effect of protecting the core material and being capable of releasing easily the core material in intestinal tract can be obtained by incorporating an enteric polymer material into the ethylcellulose coating walls of microcapsules containing core material, or incorporating a water-swellingable polymer material into the core material contained in the microcapsules and further incorporating an enteric polymer material into the ethylcellulose coating walls.

An object of the present invention is to provide enteric microcapsules being capable of releasing easily the active component (core material) in intestinal tract while protecting the core material effectively in stomach. Another object of the invention is to provide a process for the preparation of the enteric microcapsules. These and other objects and advantages of the present invention will be apparent to persons skilled in the art from the following description.

The novel enteric microcapsules of the present invention (i.e., enteric microcapsules containing an active compound as a core material, the coating walls of which

consists essentially of ethylcellulose and an enteric polymer material) can be prepared by the steps of:

- (a) dissolving ethylcellulose in a solvent,
- (b) dispersing particles of a core material in the  
5 solution thus obtained,
- (c) cooling the dispersion until coating walls  
having a viscosity of 0.1 to 50 P are formed on and  
around the particles of the core material,
- (d) adding an enteric polymer material to the  
10 dispersion,
- (e) further cooling the dispersion containing the  
enteric polymer material until the resultant embryonic  
microcapsules shrink and become solid by solvent loss  
from the coating walls, and then
- 15 (f) recovering the thus-formed microcapsules  
therefrom.

The core material used in the present invention includes pharmaceutical compounds and foodstuffs which may be in the form of a solid, gel or semi-solid. The  
20 particle size of the core material is not critical but is usually in the range of about 30 to 1,000  $\mu$ , preferably about 50 to 500  $\mu$ .

Ethylcellulose used for forming microcapsule coating walls on and around the particles of the core  
25 material has preferably an ethoxy content of about 46.5 to 55 W/W % and a viscosity of about 3 to 500 cP (the viscosity of ethylcellulose is measured in a 5 W/W %

solution in toluene-ethanol (4 : 1) at 25°C). The ethylcellulose is usually used in an amount of about 0.01 to 10 grams per gram of the core material.

The enteric polymer material to be incorporated into the ethylcellulose coating walls includes (i) an organic dicarboxylic acid ester of a hydroxyalkyl alkylcellulose or cellulose acetate; (ii) a carboxyalkyl alkylcellulose; (iii) a copolymer of an alkenylcarboxylic acid and an alkyl ester of an alkenylcarboxylic acid; (iv) a copolymer of an alkenylcarboxylic acid and two alkyl esters of an alkenylcarboxylic acid, (v) zein and (vi) shellac. Suitable examples of the organic dicarboxylic acid esters of a hydroxyalkyl alkylcellulose or cellulose acetate (i) are phthalic acid esters of a hydroxyalkyl alkylcellulose or cellulose acetate, such as hydroxyethyl ethylcellulose phthalate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, and other organic dicarboxylic esters such as cellulose acetate succinate, cellulose acetate maleate, or the like. Suitable examples of the carboxyalkyl alkylcellulose (ii) are carboxymethyl methylcellulose and carboxymethyl ethylcellulose. Suitable examples of the copolymer of an alkenylcarboxylic acid and an alkyl ester of an alkenylcarboxylic acid (iii) are copolymers of methacrylic acid and an alkyl acrylate or methacrylate, such as a copolymer of methacrylic acid and methyl acrylate, a copolymer of methacrylic acid and ethyl

acrylate, copolymer of methacrylic acid and methyl methacrylate. Suitable examples of the copolymer of an alkenylcarboxylic acid and two alkyl esters of an alkenylcarboxylic acid (iv) are copolymers of methacrylic acid, an alkyl acrylate and an alkyl methacrylate, such as a copolymer of methacrylic acid, methyl acrylate and methyl methacrylate, a copolymer of methacrylic acid, methyl acrylate and octyl acrylate.

These enteric polymer materials are preferably in the form of a finely-divided particle, particularly having a particle size of about  $300\ \mu$  or less, more particularly a particle size of  $0.1$  to  $300\ \mu$ . The enteric polymer materials are preferably used in an amount of at least about  $0.01$  gram, more preferably about  $0.05$  to  $20$  grams per gram of the coating wall-forming material (ethylcellulose).

When a water-swellable polymer material is incorporated into the core material in microcapsules wherein an enteric polymer material is incorporated in the coating walls, the release of the active compound is more promoted.

Such a water-swellable polymer material is a material which shows at least  $1.2$  times increase in weight by immersing it in water at  $37^{\circ}\text{C}$ . The water-swellable polymer material includes agar-agar, pectinic acid, alginic acid, cellulose, starch, a carboxyalkyl cellulose (e.g. carboxymethyl cellulose) or its calcium

salt, copolymers of divinylbenzene and an alkenyl-carboxylic acid (e.g. a copolymer of divinylbenzene and acrylic acid, a copolymer of divinylbenzene and methacrylic acid), a cross-linked gum arabic (e.g.

5 gum arabic cross-linked with epichlorohydrin), a cross-linked dextran (e.g. dextran cross-linked with epichlorohydrin), and a cross-linked polyalkenylcarboxylic acid (e.g. self-crosslinked polyacrylic acid, self-cross-linked methacrylic acid).

10                These water-swellaable polymer materials are preferably in the form of a finely-divided particle, particularly having a particle size of about  $300\mu$  or less, more particularly a particle size of 0.1 to  $300\mu$ . Suitable amount of the water-swellaable polymer material  
15 to be incorporated into the core material is about 1 to 99 w/w %, especially about 5 to 90 w/w %.

                 In the preparation of the microcapsules of the present invention, an ethylcellulose dispersion containing a core material is firstly prepared by  
20 dispersing a core material into a solution containing ethylcellulose as the wall-forming material. In case of ethylcellulose microcapsules containing a water-swellaable polymer material in the core material, it is preferable to previously prepare a granule of a  
25 mixture of a core material and a water-swellaable polymer material, and the core material containing a water-swellaable polymer material is dispersed into

a solution of ethylcellulose.

The solvent for dissolving ethylcellulose is a substance which can dissolve ethylcellulose with heating (i.e. at a temperature of about 75 to 80°C) but does not dissolve under cooling and further does not dissolve both of the core material and the water-swallowable polymer material. Suitable examples of the solvent are cyclohexane, a mixture of cyclohexane and n-hexane, or the like, among which cyclohexane is particularly suitable. Ethylcellulose is dissolved in such a solvent at a temperature of about 75 to 80°C. The ethylcellulose solution thus obtained has preferably a concentration of ethylcellulose of about 0.1 to 10 W/W %, more preferably about 1 to 5 W/W %. The dispersion of a core material or a core material containing a water-swallowable polymer material into an ethylcellulose solution is preferably carried out with stirring at a temperature of about 75 to 80°C. The granule of a mixture of a core material and a water-swallowable polymer material can be prepared by a conventional method such as wet-granulation method or dry-granulation method, and the particle size of the granule is not critical but is usually in the range of about 30 to 1,000  $\mu$ , preferably 50 to 500  $\mu$ .

The phase-separation of ethylcellulose from the dispersion of a core material or a core material containing water-swallowable polymer material is carried



out in the presence or absence of a phase-separation-inducing agent, i.e. by either coacervation or flocculation, and optionally in the presence of a wall-forming auxiliary and/or a surfactant.

5                   The phase-separation-inducing agent includes polyethylene, butyl rubber, polyisobutylene, and polybutadiene. The wall-forming auxiliary includes dimethyl polysiloxane, methylphenyl polysiloxane, diphenyl polysiloxane, and polystyrene-polydimethyl polysiloxane  
10 block copolymer. The surfactant includes an ester of  $C_{12-18}$  fatty acid with sorbitan (e.g. sorbitan monolaurate, sorbitan sesquilaurate, sorbitan trilaurate, sorbitan monooleate), an ester of  $C_{8-18}$  fatty acid with glycerin (e.g. glycerin monocaprylate, glycerin mono-  
15 laurate, glycerin monooleate), a phospholipid (e.g. soybean phospholipids, egg-yolk phospholipids), calcium stearyl lactate, an ester of  $C_{8-18}$  fatty acid with propylene glycol (e.g. propylene glycol monocaprylate, propylene glycol monostearate), and an ester of  $C_{12-18}$   
20 fatty acid with sucrose (e.g. sucrose mono-, di- or tristearate). These additives may be added to the ethylcellulose solution prior to dispersing the core material in said solution. The additives are used in a concentration of about 0.01 to 10 W/V % (phase-separation-inducing agent), about 0.01 to 10 W/V % (wall-  
25 forming auxiliary), and about 0.001 to 10 W/V % (surfactant), respectively.

The phase-separation of ethylcellulose is preferably carried out by cooling the dispersion at a rate of about 0.05 to 4°C/minute, especially 0.1 to 2°C/minute. When an enteric polymer material is incorporated into the ethylcellulose coating walls, it is added with stirring to the dispersion during the cooling step, particularly at the stage where coating walls of ethylcellulose in the form of "gel" is formed on and around the particles of the core material and the thus-formed coating walls have still fluidity in some extent (i.e. have a viscosity of 0.1 to 50 P, especially 1 to 10 P). More especially, since the coating walls having a fluidity is formed on an around the core material by cooling the dispersion to about 55 to 75°C, especially about 65°C (while it may somewhat vary depending on the scale of method and cooling rate, etc.), it is preferable to add the enteric polymer material to the dispersion when cooled to said temperature. The enteric polymer material thus added is appropriately penetrated and dispersed into the coating walls. After adding the enteric polymer material, the dispersion is further cooled to a temperature not higher than 40°C (e.g. 30 to 20°C), and thereby, the formed embryonic microcapsules are shrunk and become solid by solvent loss from the coating walls, thus giving stable ethylcellulose microcapsules.

The microcapsules thus obtained may be

recovered in conventional manner, such as decantation, centrifugation, filtration and so forth, wherein the microcapsules do not adhere or coagulate each other. The microcapsules thus recovered may, if required,  
5 be washed with a solvent such as cyclohexane, petroleum ether, n-hexane, etc. and then dried in conventional manner (e.g. by a hot-air drying method or heat transfer drying method).

The microcapsules of the present invention  
10 can be applied to not only pharmaceutically active compounds or medicaments but also other various substances such as veterinary drugs, foodstuffs, or the like. The pharmaceutically active compounds or medicaments, to which the microcapsules of the present invention and the process for the preparation thereof can be  
15 applied, are, for example, vitamins (e.g. ascorbic acid), amino acids (e.g. potassium aspartate, magnesium aspartate), peptides (e.g. insulin), chemotherapeutics (e.g. sulfamethizole), antibiotics (e.g. benzylpenicillin potassium salt), respiratory stimulants (e.g. dimeflin hydrochloride),  
20 antitussives and expectorants (e.g. tipecidine dibenzoate, bromhexine hydrochloride, trimetoquinol hydrochloride), anti-tumor agents (e.g. 5-fluorouracil, bleomycin hydrochloride), autonomic agents (e.g. N-butylscopolammonium bromide), neuro-psychotropic agents (e.g. calcium N-( $\gamma$ ,  $\gamma$ -dihydroxy- $\beta$ ,  $\beta$ -dimethylbutyryl)- $\gamma$ -aminobutyrate), local anesthetics (e.g. oxethazone), muscle relaxants (e.g.

phenprobamate), agents affecting digestive organs (e.g. methylmethionine sulfonium chloride, 1,1-dimethyl-5-methoxy-3-(dithien-2-ylmethylene)piperidinium bromide, precipitated calcium carbonate, trimebutine maleate),  
5 anti-histaminics (e.g. diphenhydramine hydrochloride),  
antidotes (e.g. D-penicillamine, diferoxamine mesylate),  
hypnotics and sedatives (e.g. flurazepam hydrochloride),  
antiepileptics (e.g. sodium valproate), antipyretics,  
analgesics and anti-inflammatory agents (e.g. acetyl-  
10 salicylic acid, indometacin, naproxen), cardiotonics  
(e.g. digoxin, proscillaridin), antiarrhythmic agents  
(e.g. oxprenolol hydrochloride), diuretics (e.g. penfluzide),  
vasodilators (e.g. diltiazom hydrochloride), antilipaemics  
(e.g. sodium dextran sulfate), nutrients, tonics and  
15 alteratives (e.g. calcium L-aspartate), anticoagulants  
(e.g. heparin calcium), agents for liver disease (e.g.  
phosphorylcholine chloride calcium salt), antidiabetic  
agents (e.g. carbutamide), antihypertensives (e.g.  
clonidine hydrochloride), or the like. The medicament  
20 to be microencapsulated may also be a composition containing such pharmaceutically active compound together with an inert excipient or vehicle.

When the microcapsules containing an enteric  
polymer material in the coating walls of the present  
25 invention are administered, the release of the active  
compound does not occur in stomach, but the enteric  
polymer material is easily dissolved in intestinal

tract and thereby the microcapsules become porous. Accordingly, the liquid in intestinal tract can easily penetrate into the microcapsules and thereby the release of active compound is promoted. Thus, when pharmaceutical compounds which are decomposed or in-  
5 activated by gastric juice or can easily be absorbed in intestinal tract are microencapsulated by the present invention, they are sufficiently protected in stomach and are rapidly released in intestinal tract.  
10 Besides, when a water-swellable polymer material is incorporated into the core material, the active compound is likewise protected in stomach, but the enteric polymer material in the ethylcellulose coating walls is rapidly dissolved in intestinal tract to make the coating walls  
15 porous, by which the penetration of liquid into the core material is promoted and then the water-swellable polymer material absorbs the liquid and swells. Owing to the swelling pressure, the core material is finely cracked and thereby release of the active compound is  
20 further promoted. That is, by coaction of the phenomenon that the coating walls become porous and the capillarity by fine cracking in the core material, the release of the active compound in intestinal tract is promoted. In addition to the above advantages, the microcapsules  
25 of the present invention have an appropriately improved ethylcellulose coating walls by incorporating an enteric polymer material into the coating walls, by which the

microcapsules show excellent compatibility with various carrier and also excellent free-flowing characteristics and further the microcapsules can easily be tableted without undesirable sticking or capping. The microcapsules of the present invention show also less unpleasant feeling when administered.

The present invention is illustrated by the following Experiments and Examples, wherein "part" means "part by weight" unless specified otherwise. Throughout the specification and claims, the terms "alkyl" and "alkenyl" should be interpreted as referring to alkyl having one to 8 carbon atoms, preferably one to 4 carbon atoms and alkenyl having 2 to 4 carbon atoms, respectively.

#### Experiment I

Pyridoxal phosphate-containing microcapsules (an enteric polymer material being incorporated into the coating walls) were prepared according to the following methods. Then, the yield of microcapsules thus obtained, the content of the active ingredient contained in the microcapsules, the release rate (%) of the active ingredient therefrom in the first liquid as defined in the Pharmacopoeia of Japan 10th-Edition, Disintegration Test, and the 50 % release time ( $T_{50}$ ) (i.e. a period of time which was necessary to release 50 % of the active ingredient from the microcapsules) in the second liquid were examined, respectively.

(i) Core material:

To a mixture of pyridoxal phosphate (150 parts) and lactose (129 parts) was added a solution of hydroxypropyl methylcellulose phthalate (21 parts) in 80 % aqueous ethanol (30 parts), and the mixture was kneaded in a usual manner to form granules. The granules were dried and regulated to a particle size of 105 to 210  $\mu$ .

(ii) Preparation of microcapsules:

To cyclohexane (600 ml) were added a silicone resin (conformable to the requirements of 4th Official Compendium of Food Additives in Japan, i.e. a mixture of dimethyl polysiloxane (viscosity: 100 to 1,100 cSt at 25°C) and 3 to 15 % by weight of silicon dioxide) (18 g) and ethylcellulose (ethoxy content: 48.5 %, viscosity: 100 cP) (10 g) and the mixture was dissolved by heating at 80°C. After dispersing a core material (40 g) to the solution, the dispersion was cooled with stirring at 400 r.p.m. When the temperature became to about 65°C, finely divided particles of hydroxypropyl methylcellulose phthalate were added in an amount as shown in the following Table 1 in order to incorporate them into the coating walls and then the mixture was cooled to room temperature. The microcapsules thus formed were separated, washed with n-hexane and dried. Said microcapsules were passed through JIS (Japanese Industrial Standard) standard sieve (350  $\mu$  aperture) to give pyridoxal phosphate-containing microcapsules

which met the requirements of "powders" specified in the Pharmacopoeia of Japan 10th-Edition.

As a reference, microcapsules were prepared in the same manner as described above except that no  
5 hydroxypropyl methylcellulose phthalate was added.

(iii) Results:

The results are shown in Table 1. As is clear from the results, when the addition amount of the hydroxy-  
propyl methylcellulose phthalate was larger, the release  
10 of the active ingredient in the second liquid was more promoted.



Table 1

Experiment No.	Amount of hydroxypropyl methylcellulose phthalate *	Yield of micro-capsules (g)	Content of active ingredient in capsules (%)	Active ingredient released after 2 hrs. in the first liquid (%)	T <sub>50</sub> in the second liquid (minute)
The present invention	10	58	33.4	9.8	68
	50	95	21.0	8.0	36
	100	147	13.5	10.1	10
Reference	-	49	40.8	8.4	260

\*) It had methoxy content: 22.2 %, hydroxypropoxy content: 7.5 %, and carboxybenzoyl content: 21.0 %.

Experiment II

Pyridoxal phosphate-containing microcapsules (a water-swellable polymer material being incorporated into the core material, and an enteric polymer material being incorporated into the coating walls) were prepared, and the yield of microcapsules, the content of the active ingredient contained in the microcapsules, the release rate of the active ingredient therefrom in the first liquid and  $T_{50}$  in the second liquid were examined, likewise.

## (i) Core material:

To a mixture of pyridoxal phosphate (150 parts), carboxymethyl cellulose ("a" part) and lactose (129 - "a" parts) was added a solution of a white dextrin (21 parts) in 40 % aqueous ethanol (21 parts), and the mixture was kneaded in a usual manner to give granules. The granules were dried and regulated to a particle size of 105 to 210  $\mu$ .

## (ii) Preparation of microcapsules:

To cyclohexane (600 ml) were added dimethyl polysiloxane (viscosity: 1,000,000 cSt at 25°C) (18 g) and ethylcellulose (ethoxy content: 47.5 %, viscosity: 110 cP) (10 g), and the mixture was dissolved by heating at 80°C. After dispersing a core material (40 g) to the solution, the dispersion was cooled with stirring at 400 r.p.m. When the temperature became to about 65°C, finely divided particles (50 g) of hydroxypropyl methyl-

cellulose (methoxy content: 21.4 %, hydroxypropoxy content: 6.7 %, carboxybenzoyl content: 28.5 %) in order to incorporate them into the coating walls and then the mixture was cooled to room temperature. The  
5 microcapsules thus formed were separated, washed with n-hexane and dried. Said microcapsules were passed through JIS standard sieve (350  $\mu$  aperture) to give pyridoxal phosphate-containing microcapsules which met the requirements of "powders".

10

(iii) Results:

The results are shown in Table 2.

Table 2

Experiment No.	Carboxymethyl cellulose ("a" part)	Yield of micro-capsules (g)	Content of active ingredient in capsules (%)	Active ingredient released after 2 hrs. in the first liquid (%)	T <sub>50</sub> in the second liquid (minute)
The present invention					
1	129	98	20.1	9.8	8
2	60	96	20.7	10.1	19
3	-	97	20.6	9.2	40

Example 1

(1) To a mixture of diltiazem hydrochloride (50 parts) and lactose (30 parts) was added a solution of polyvinyl acetate (20 parts) in ethyl acetate (20 parts), and the mixture was kneaded in a usual manner to give granules. The granules were dried and regulated to a particle size of 105 to 210  $\mu$ .

(2) To cyclohexane (600 ml) were added the same silicone resin as used in Experiment I (18 g) and the same ethylcellulose as used in Experiment I (15 g), and the mixture was dissolved by heating at 80°C. After dispersing the core material as obtained in the above (1) (15 g) to the solution, the dispersion was cooled with stirring at 400 r.p.m. When the temperature became to about 65°C, the enteric polymer material as shown in Table 3 (45 g) was added in order to incorporate it into the coating walls and then the mixture was cooled to room temperature. The microcapsules thus formed were washed with n-hexane and dried. Said microcapsules were passed through JIS standard sieve (350  $\mu$  aperture) to give diltiazem hydrochloride-containing microcapsules which met the requirements of "powders".

Table 3

Enteric polymer material	Yield of microcapsules (g)	Content of active ingredient in microcapsules (%)
1 Methyl acrylate-methacrylic acid copolymer (1 : 1 by mole)	72	10.3
2 Methyl acrylate-methacrylic acid-methyl methacrylate copolymer (1 : 1.2 : 1.2 by mole)	67	11.1
3 Methyl methacrylate-methacrylic acid copolymer (52.4 : 47.6 by weight)	70	10.7
4 Methyl methacrylate-methacrylic acid copolymer (70.8 : 29.2 by weight)	71	10.5
5 Carboxymethyl-ethyl-cellulose (substitution degree of carboxymethyl: 0.65, substitution degree of ethoxy: 2.1)	74	10.1
6 Cellulose acetate phthalate (acetyl content: 20.8 %, carboxybenzoyl content: 34.5 %)	70	10.7
7 Shellac	71	10.1
8 Zein	69	10.7
9 Methacrylic acid-ethyl acrylate copolymer (1 : 1 by mole)	71	10.0

Example 2

(1) To a mixture of trimethoquinol hydrochloride (chemical name: *l*-1-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride) (25 parts),  
5 lactose (45 parts), white dextrin (10 parts) and a water-swallowable polymer material as shown in Table 4 (20 parts) was added a 40 % aqueous ethanol (10 parts), and the mixture was kneaded in a usual manner to give granules. The granules were dried and regulated to a particle  
10 size of 105 to 210  $\mu$ .

(2) To cyclohexane (600 ml) were added a mixture of two polyisobutylenes (molecular weight: 50,000 and 1,200,000, respectively, 1 : 1 by weight) (18 g) and the same ethylcellulose as used in Experiment  
15 I (12 g), and the mixture was dissolved by heating at 80°C. After dispersing the core material as obtained in the above (1) (48 g) to the solution, the dispersion was cooled with stirring at 400 r.p.m. When the temperature became to about 65°C, cellulose acetate phthalate  
20 (acetyl content: 20.8 %, carboxybenzoyl content: 34.5 %) (60 g) was added in order to incorporate it into the coating walls and then the mixture was cooled to room temperature. The microcapsules thus formed were separated washed with n-hexane and dried. Said microcapsules were  
25 treated in the same manner as described in Example 1 to give trimethoquinol hydrochloride-containing microcapsules.

Table 4

Water-swellable polymer material	Degree of swelling	Yield of microcapsules (g)	Content of active ingredient (%)
Agar-agar	4.0	115	10.3
Carboxymethyl-cellulose calcium	2.1	117	10.2
Pectinic acid	3.5	114	10.5
Gum arabic cross-linked with epichlorohydrin	8.5	118	10.1
Dextran cross-linked with epichlorohydrin	15	109	10.9
Divinylbenzene-acrylic acid copolymer	4.4	113	10.6
Self-crosslinked polyacrylic acid	20	108	11.1
Potato starch	1.4	117	10.1
Carboxymethyl-cellulose	2.3	110	10.9
Crystalline cellulose	1.2	115	10.3

20

Example 3

To cyclohexane (600 ml) were added polyethylene (molecular weight: 7,000) (18 g) and the same ethyl-cellulose as used in Experiment I (12 g) and the mixture was dissolved by heating at 80°C. After dispersing 1-methyl-5-methoxy-3-(dithien-2-ylmethylene)piperidium

25



hydrobromide (I) (particle size: 105 - 210  $\mu$ ) (48 g)  
to the solution, the dispersion was cooled with stirring  
at 400 r.p.m. When the temperature became to about 65°C,  
carboxymethyl ethylcellulose (substitution degree of  
5 carboxymethyl: 0.55, substitution degree of ethoxy: 2.2)  
(60 g) was added in order to incorporate it into the  
coating walls, and the mixture was cooled to room  
temperature. The microcapsules thus formed were treated  
in the same manner as described in Example 2-(2) to give  
10 the active compound (I)-containing microcapsules (116 g)  
which met the requirements of "powders" and had a content  
of the active compound (I) of 40.1 %.

claims

1. In ethylcellulose microcapsules comprising  
(i) particles of a core material and (ii) ethylcellulose  
coating walls deposited on and around said particles of  
5 the core material, the improvement wherein an enteric  
polymer material is incorporated into the ethylcellulose  
coating walls of the microcapsules.

2. The microcapsules according to claim 1,  
wherein the enteric polymer material is a member selected  
10 from the group consisting of an organic dicarboxylic acid  
ester of a hydroxyalkyl alkylcellulose or cellulose  
acetate, a carboxyalkyl alkylcellulose, a copolymer of  
an alkenylcarboxylic acid and an alkyl ester of an  
alkenylcarboxylic acid, a copolymer of an alkenyl-  
15 carboxylic acid and two alkyl esters of an alkenyl-  
carboxylic acid, zein and shellac.

3. The microcapsules according to claim 1,  
wherein the enteric polymer material is a member selected  
from the group consisting of a phthalic acid ester of a  
20 hydroxyalkyl alkylcellulose or cellulose acetate, a  
carboxyalkyl alkylcellulose, a copolymer of methacrylic  
acid and an alkyl acrylate, a copolymer of methacrylic  
acid and an alkyl methacrylate, a copolymer of meth-  
acrylic acid, an alkyl acrylate and an alkyl meth-  
25 acrylate, zein and shellac.

4. The microcapsules according to claim 1,  
wherein the enteric polymer material is a member selected

from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethyl ethylcellulose, copolymer of methacrylic acid and methyl acrylate, copolymer of methacrylic acid and ethyl acrylate, copolymer of methacrylic acid and methyl methacrylate, copolymer of methacrylic acid, methyl acrylate and methyl methacrylate, zein and shellac.

5. The microcapsules according to either one of claims 1 through 4, wherein the enteric polymer material is contained in the coating walls of ethylcellulose in an amount of at least 0.01 gram per gram of ethylcellulose.

6. The microcapsules according to either one of claims 1 through 4, wherein the enteric polymer material is contained in the coating walls of ethylcellulose in an amount of 0.05 to 20 grams per gram of ethylcellulose.

7. The microcapsules according to claim 6, wherein the ethylcellulose has an ethoxy content of 46.5 to 55 W/W %.

8. The microcapsules according to claim 6, wherein the ethylcellulose has an ethoxy content of 46.5 to 55 W/W % and a viscosity [measured at 25°C with respect to a 5 W/W % solution in toluene-ethanol (4 : 1)] of 3 to 500 cP.

9. The microcapsules according to claim 7,

wherein particles of the core material contain a water-swella-  
ble polymer material which shows at least 1.5  
times increase in weight by immersing it in water at  
37°C.

5                   10. The microcapsules according to claim 9,  
wherein the water-swella-ble polymer is a member selected  
from the group consisting of agar-agar, pectinic acid,  
alginic acid, cellulose, starch, a carboxyalkyl cellu-  
lose, a carboxyalkyl cellulose calcium, a copolymer of  
10 divinylbenzene and an alkenylcarboxylic acid, a cross-  
linked gum arabic, a cross-linked dextran, and a cross-  
linked polyalkenylcarboxylic acid.

                  11. The microcapsules according to claim 9,  
wherein the water-swella-ble polymer is a member selected  
15 from the group consisting of agar-agar, pectinic acid,  
alginic acid, cellulose, starch, carboxymethyl cellulose,  
carboxymethyl cellulose calcium, copolymer of divinyl-  
benzene and acrylic acid, gum arabic cross-linked with  
epichlorohydrin, dextran cross-linked with epichlorohydrin,  
20 and self-crosslinked polyacrylic acid.

                  12. A method of preparing ethylcellulose  
microcapsules which comprises the steps of:

- (a) dissolving ethylcellulose in a solvent,
- (b) dispersing particles of a core material in the  
25 solution thus obtained,
- (c) cooling the dispersion until coating walls  
having a viscosity of 0.1 to 50 P are formed on and

around the particles of the core material,

(d) adding an enteric polymer material to the dispersion,

(e) further cooling the dispersion containing the  
5 enteric polymer material until the resultant embryonic microcapsules shrink and become solid by solvent loss from the coating walls, and then

(f) recovering the thus-formed microcapsules therefrom.

10 13. The method according to claim 12, wherein the enteric polymer material is a member selected from the group consisting of an organic dicarboxylic acid ester of a hydroxyalkyl alkylcellulose or cellulose acetate, a carboxyalkyl alkylcellulose, a copolymer of  
15 an alkenylcarboxylic acid and an alkyl ester of an alkenylcarboxylic acid, a copolymer of an alkenylcarboxylic acid and two alkyl esters of an alkenylcarboxylic acid, zein and shellac.

20 14. The method according to claim 12, wherein the enteric polymer material is a member selected from the group consisting of a phthalic acid ester of a hydroxyalkyl alkylcellulose or cellulose acetate, a carboxyalkyl alkylcellulose, a copolymer of methacrylic acid and an alkyl acrylate, a copolymer of methacrylic  
25 acid, an alkyl acrylate and an alkyl methacrylate, zein and shellac.

15. The method according to claim 12, wherein the enteric polymer material is a member selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethyl  
5 ethylcellulose, copolymer of methacrylic acid and methyl acrylate, copolymer of methacrylic acid and ethyl acrylate, copolymer of methacrylic acid and methyl methacrylate, copolymer of methacrylic acid, methyl acrylate and methyl methacrylate, zein and shellac.

10 16. The method according to either one of claims 12 through 15, wherein ethylcellulose having an ethoxy content of 46.5 to 55 W/W % is used.

15 17. The method according to either one of claims 12 through 15, wherein ethylcellulose having an ethoxy content of 46.5 to 55 W/W % and a viscosity [measured at 25°C with respect to a 5 W/W % solution in toluene-ethanol (4 : 1)] of 3 to 500 cP is used.

18. The method according to claim 16, wherein the solvent is cyclohexane.

20 19. The method according to claim 18, wherein the ethylcellulose is used in an amount of 0.01 to 10 grams per gram of core material.

25 20. The method according to claim 18, wherein the enteric polymer material is used in an amount of at least 0.01 gram per gram of ethylcellulose.

21. The method according to claim 18, wherein the enteric polymer material is used in an amount of

0.05 to 20 grams per gram of ethylcellulose.

22. The method according to claim 18, wherein particles of the core material having 30 to 1,000  $\mu$  are dispersed in the solution of ethylcellulose, and the enteric polymer material having a particle size not more than 300  $\mu$  is added at the stage when the coating walls have a viscosity of 0.1 to 50 P.

23. The method according to claim 22, wherein particles of the core material contain a water-swella-  
10 polymer material.

24. The method according to claim 23, wherein the water-swella-  
15 ble polymer material is a member selected from the group consisting of agar-agar, pectinic acid, alginic acid, cellulose, starch, a carboxyalkyl cellulose, a carboxyalkyl cellulose calcium, a copolymer of divinyl-  
benzene and an alkenylcarboxylic acid, a cross-linked gum arabic, a cross-linked dextran, and a cross-linked polyalkenylcarboxylic acid.

25. The method according to claim 23, wherein the water-swella-  
20 ble polymer material is a member selected from the group consisting of agar-agar, pectinic acid, alginic acid, cellulose, starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, copolymer of divinyl-  
benzene and acrylic acid, gum arabic cross-linked with  
25 epichlorohydrin, dextran cross-linked with epichloro-  
hydrin, or self-crosslinked polyacrylic acid.

26. The method according to either one of

claims 22 through 25, wherein the ethylcellulose is dissolved in cyclohexane at a temperature of about 75 to 80°C, the dispersion is cooled at a rate of 0.05 to 4°C/minute, and the enteric polymer material is  
5 added to the dispersion at a temperature of about 55 to 75°C.

27. The method according to either one of claims 22 through 25, wherein at least one member selected from a phase-separation-inducing agent, an  
10 organosilicon polymer compound and a surfactant is further added to the solution of ethylcellulose.





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# EUROPEAN SEARCH REPORT

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Application number

EP 82 10 9335

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
X	--- GB-A-2 009 698 (THE BRITISH PETROLEUM CO.) * page 2, lines 67-84 *	1-6	B 01 J 13/02 A 61 K 9/52
A	--- US-A-3 960 757 (MASATAKA MORISHITA et al.) * column 1, lines 40-44; column 3, lines 5-30, 55-68; column 4, lines 1-31 *	1,2,3	
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The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 10-01-1983	Examiner KERRES P.M.G.
<b>CATEGORY OF CITED DOCUMENTS</b>			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons  & : member of the same patent family, corresponding document	

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A	US-A-3 247 066 (G. MILOSOVICH) * column 4, lines 1-27; column 5, lines 10-73 *	1, 9, 10, 11	
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			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 10-01-1983	Examiner KERRES P.M.G.
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>			